



## Review Article

# The outbreak of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): A review of the current global status

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## ABSTRACT

There is currently an ongoing worldwide pandemic of a novel virus belonging to the family of Coronaviruses (CoVs) which are large, enveloped, plus-stranded RNA viruses. Coronaviruses belong to the order of Nidovirales, family of Coronavirinae and are divided into four genera: alphacoronavirus, betacoronavirus, gammacoronavirus and deltacoronavirus. CoVs cause diseases in a wide variety of birds and mammals and have been found in humans since 1960. To date, seven human CoVs were identified including the alpha-CoVs HCoV-NL63 and HCoV-229E and the beta-CoVs HCoV-OC43, HCoV-HKU1, the severe acute respiratory syndrome-CoV (SARS-CoV), the Middle East respiratory syndrome-CoV (MERS-CoV) and the novel virus that first appeared in December 2019 in Wuhan, China, and rapidly spread to 213 countries as of the writing this paper. It was officially named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the international committee on taxonomy of viruses (ICTV) and the disease's name is COVID-19 for coronavirus disease 2019. SARS-CoV-2 is very contagious and is capable of spreading from human to human. Infection routes include droplet and contact, and aerosol transmission is currently under investigation. It is associated with a respiratory illness that may cause severe pneumonia and acute respiratory distress syndrome (ARDS). SARS-CoV-2 became an emergency of international concern. As of July 12, 2020, the virus has been responsible for 12,698,995 confirmed cases and 564,924 deaths worldwide and the number is still increasing. Up until now, no specific treatment has yet been proven effective against SARS-CoV-2. Since the beginning of this outbreak, several interesting papers on SARS-CoV-2 and COVID-19 have been published to report on the phylogenetic evolution, epidemiology, pathogenesis, transmission as well as clinical characteristics of COVID-19 and possible treatments agents.

This paper is a systematic review of the available literature on SARS-CoV-2. It was performed in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and aims to help readers access the latest knowledge surrounding this new infectious disease and to provide a reference for future studies.

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## Introduction

Coronaviruses (CoV) are the largest known RNA viruses. Their size varies from 65 to 125 nm in diameter and their nucleic acid genome is single-stranded RNA, size ranging from 26 to 32 kb in length [1]. Since 1960, six coronaviruses have been found to cause diseases in humans; SARS-CoV-2 is the seventh one, after SARS-CoV and MERS-CoV [2]. While HKU1, NL63, OC43 and 229E are associated with mild symptoms in humans, SARS-CoV, MERS-CoV, and SARS-CoV-2, belonging to the betacoronavirus genus, cause severe to deadly pneumonia in humans [3]. Fever, dry cough, difficulty breathing and fatigue usually accompany this pneumonia [4,5]. The fatality rates of SARS-CoV, MERS-CoV and SARS-CoV-2 are 9.5%, 34.4%, and 2.3% respectively [6]. COVID-19 shows some particular pathogenic, epidemiological and clinical features which have are not completely understood to date as well as its wide and high transmission in the community versus nosocomial spread of SARS and MERS and its milder infection and low mortality compared to the severe phenotype and higher mortality caused by the two others viruses [7]. To date, no therapeutic or vaccines were approved against any of the known human coronaviruses and only protective measures were put in place. Based on the current published literature, we summarize in this paper the origin of this novel virus and its life cycle, the clinical characteristics of the disease, the possible transmission routes, the pathogenesis, the prevention measures and the undergoing treatments of this emerging infectious disease.

## Methods

### Search strategy

The present study was conducted following the PRISMA guidelines [8]. We performed a systematic search for accessible peer-reviewed and full articles published from December 2019 to May 2020. The literature search was updated in July 2020 while reviewing the paper prior to its resubmission. Articles for review were selected from the following databases MEDLINE (PubMed), Web of Science and Google Scholar. The search terms included combinations of “COVID-19, SARS-CoV-2, new coronavirus, emergence, symptoms, multiplication cycle, transmission, diagnosis tests, prevention, and treatment”. Full-text versions of the included papers were retrieved. The reference lists of relevant studies were also assessed.

### Inclusion and exclusion criteria

Inclusion and exclusion criteria were recorded following PRISMA guidelines presented in the form of a PRISMA flow diagram (Fig. 1). Briefly, the retrieved literature was imported into Endnote software (v. × 9.0) and screened for exclusion criteria. First, duplicate literature was removed by Endnote, and then obviously inappropriate ones were eliminated based on the title and abstract. Finally, remaining inappropriate entries were eliminated by reading the full articles. The exclusion criteria for articles were non-English studies, entries with only an abstract, those with no relevant topic, and studies containing no useful or duplicated data from previously published studies. The inclusion criteria are articles reporting confirmed SARS-CoV-2 positive patients, and studies presenting original data as well as clear and precise end-point outcomes.

### Data extraction and synthesis

The authors independently extracted important information from each article fulfilling the inclusion criteria and reviewed each paper to verify the accuracy and coherence of collected data. Arguments or disagreements were resolved following discussions. The consensus extracted data were synthesized in the present paper. Ethical approval was not required for this review of existing peer-reviewed papers.

## Results

We identified 170 papers through PubMed, Web of science and Google Scholar databases and 20 papers through reference cross-check and internet research of conference abstracts. After duplicate removal, a total of 130 papers were screened for relevance. Abstracts and titles screening identified 32 studies that met the inclusion criteria. After the full-text analyses, 12 of these studies were excluded. Hence, twenty studies were eligible according to our criteria and were included in this review (Fig. 1).

### SARS-CoV-2 emergence

Coronaviruses have been described as causing several systemic infections in their selected animal host [9]. However, some of them can adapt dramatically and jump the species barrier by natural recombination causing epidemics or pandemics. Infection in human often leads to severe clinical symptoms and high mortality (<https://www.who.int/emergencies/mers-cov/en/>). We present

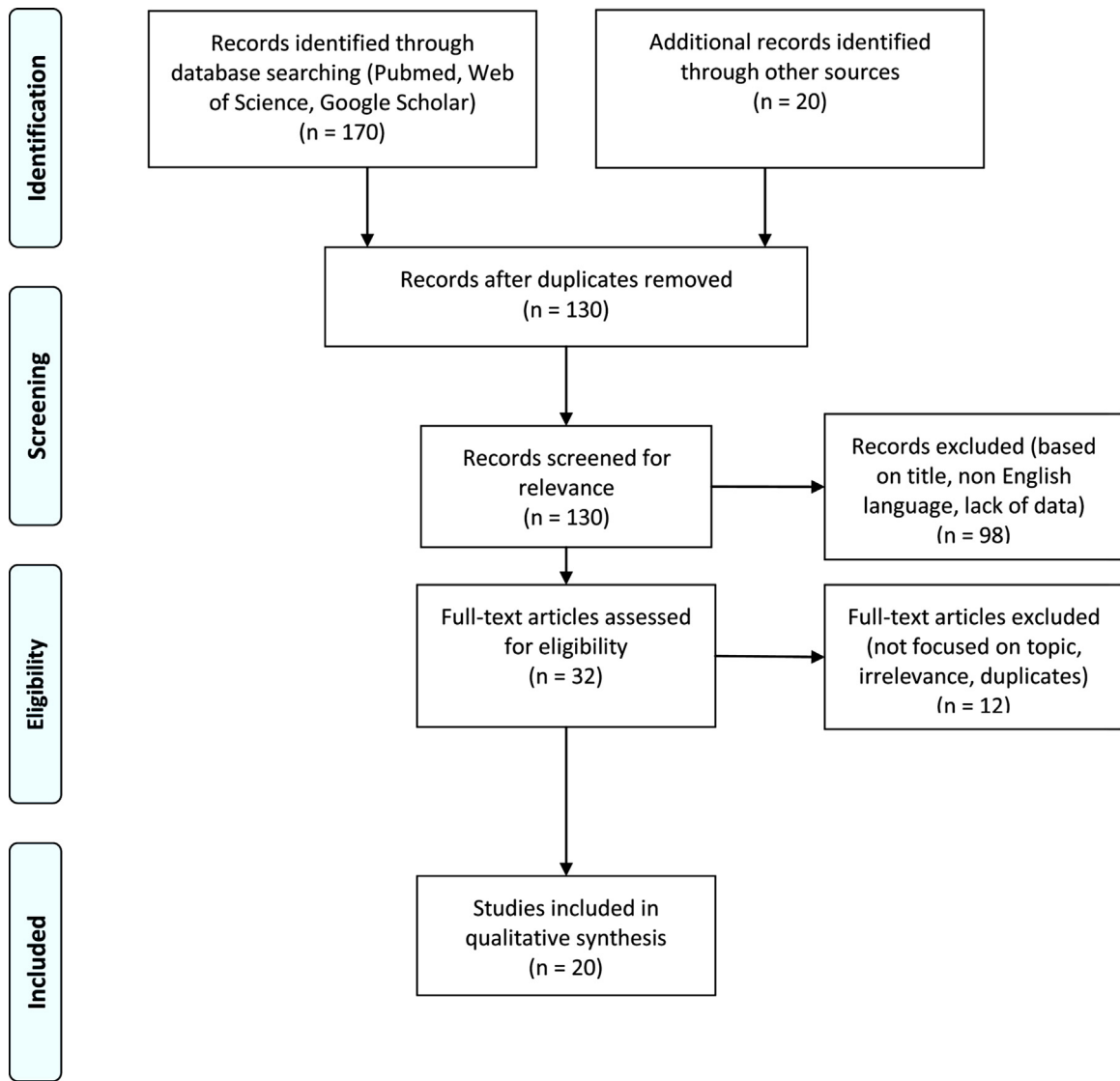


Fig. 1. PRISMA flowchart of literature search strategy.

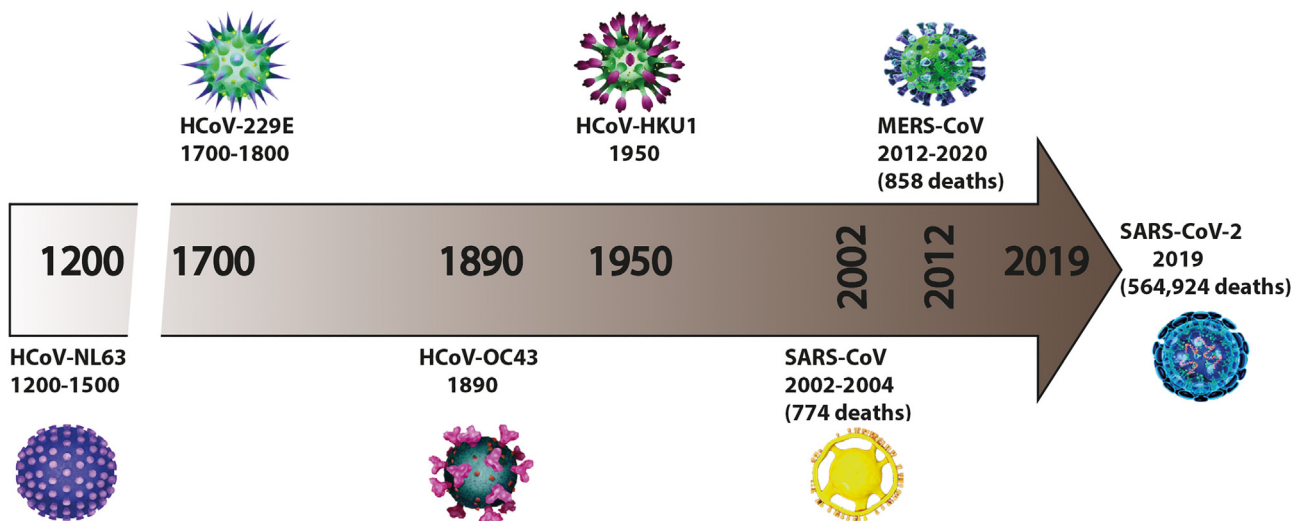
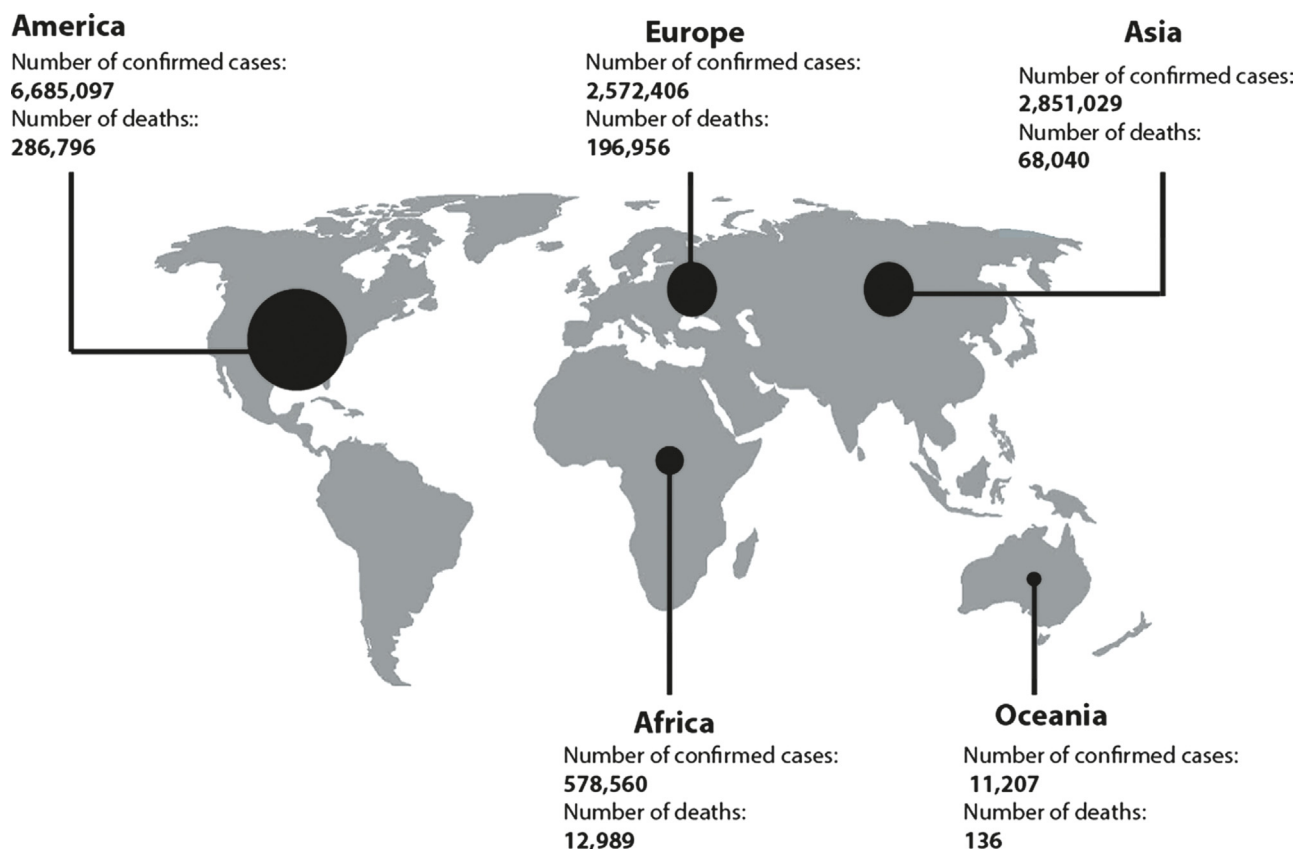


Fig. 2. Emergence of human coronaviruses: As of July 12, 2020, seven CoVs are known to be human pathogens including the alpha-CoVs HCoVs-NL63 (1200-1500) and HCoVs-229E (1700-1800) and the beta-CoVs HCoVs-OC43 (1890), HCoVs-HKU1 (1950), severe acute respiratory syndrome-CoV (SARS-CoV) (2002), Middle East respiratory syndrome-CoV (MERS-CoV) (2012) and the novel SARS-CoV-2 (2019).



**Fig. 3.** SARS-CoV-2 situation update worldwide: As of July 12, 2020, 12,698,995 cases of COVID-19 have been reported in the world including 564,924 deaths. The most affected continent is the America with 6,685,097 confirmed cases and 286,796 deaths on this day (<https://www.ecdc.europa.eu/>).

**Table 1**

Comparative analysis of SARS-CoV, MERS-CoV, and SARS-CoV-2.

Coronavirus	SARS-CoV	MERS-CoV	SARS-CoV-2
Emergency year	2002	2013	2019
Emergency area	Guangdong province, China	Arabian peninsula	Wuhan, China
Number of infected countries	29	27	213
Animal reservoir	Bat	Bat	Bat
Intermediate host	Palm civets	Camels	Unknown
Incubation time in humans (days)	2–7	2–14	2–14
Caused disease	Severe acute respiratory syndrome (SARS)	Middle East respiratory syndrome (MERS)	Coronavirus disease 2019 (COVID-19)
Clinical symptoms	Malaise, diarrhea, cough, fever and shortness of breath	Pneumonia, acute respiratory distress syndrome, renal failure	Cough, fever and shortness of breath
Number of infected patients	8098	2494	3,646,304
Number of deaths	776	858	252,425
Entry receptor in human cells	Angiotensin-converting enzyme 2 (ACE2)	Dipeptidyl peptidase 4 (DPP4)	Angiotensin-converting enzyme 2 (ACE2)
Used therapy	Supportive care	Supportive care	Supportive care

in Fig. 2 the appearance of the seven human coronaviruses over the time (Fig. 2). In 2002, in Guangdong (China), the SARS-CoV virus emerged and spread to the five continents infecting 8098 people and causing 774 deaths (9.5% of cases). In 2012, MERS-CoV emerged in the Arabian Peninsula infecting 2494 people in 27 countries and causing 858 deaths (34.4% of cases) [10]. In late December 2019, SARS-CoV-2 emerged in a seafood market (where several wildlife species are sold including bats, rabbits, snakes, birds and frogs) in Wuhan City, Hubei province, China [11]. As of July 12, 2020, this virus has been responsible for 12,698,995 confirmed cases and 564,924 deaths worldwide (2.3%). SARS-CoV-2 spread rapidly to 213 countries (at the time of revision), and the most affected continents are the America and Europe with 6,685,097 and 2,572,406 confirmed cases respectively since 31 December

2019 and as of July 12, 2020. In America, 286,796 persons were died and 196,096 ones in Europe until this day (<https://www.ecdc.europa.eu/>) (Fig. 3). On January 30, 2020, the World Health Organization (WHO) declared the SARS-CoV-2 epidemic as a public health emergency of international concern [12]. On March 11, 2020, the WHO issued an announcement of the change in COVID-19's status from an epidemic to pandemic disease. It was suggested that MERS-CoV, SARS-CoV and SARS-CoV-2 originated from bats [13]. Phylogenetic analyses showed that SARS-CoV-2, SARS-CoV and SARS-like coronaviruses isolated in bats belong to a different clade than MERS-CoV, with a complete genome nucleotide identity between SARS-CoV-2 and SARS-CoV of 79.5% and between SARS-CoV-2 and bat SARS coronavirus (SARSr-CoV-RaTG13) of 96% [13,14]. Palm civets and racoon dogs were identified as the likely

reservoir host fuelling spillover to humans for SARS-CoV [15,16], while MERS-CoV's intermediate host is unequivocally dromedary camels [17,18]. For SARS-CoV-2, pangolins and snakes are thought to be potential intermediate hosts but this requires further confirmation [19]. More evidence is needed to confirm the origin of this novel virus and its transmission to humans, to understand the best way to prevent and slow down its transmission and to better control of future zoonotic events. In Table 1, we summarize the principal characteristics of SARS-CoV, MERS-CoV and SARS-CoV-2. Briefly, bats seem to be the common natural origin of SARS-CoV-2, SARS-CoV and MERS-CoV. The clinical features of the three viruses are quite similar. However, unlike SARS-CoV and MERS-CoV, SARS-CoV-2 is more contagious and spreads rapidly, currently affecting more than 213 countries (<https://www.who.int>). SARS-CoV-2 uses the SARS-CoV receptor angiotensin-converting enzyme 2 (ACE2) on host target cells; however, MERS-CoV binds to the dipeptidyl peptidase 4 receptor (DDP4) [20]. According to the latest studies, SARS-CoV-2 has the highest number of casualties but its mortality rate is lower (2.3%) compared to SARS-CoV (9.5%) and MERS (34.4%) [6]. Therefore, SARS-CoV-2 resembles both SARS-CoV and MERS-CoV, but appears unique in its high transmission rates.

### Clinical features and pathogenesis

COVID-19 is a highly contagious disease. Its clinical manifestations range from mild to severe but most infected cases present a mild form of the disease and therefore have no severe clinical features [21]. Based on current data, 81% of the cases exhibit mild symptoms and 1.2% are asymptomatic (<http://weekly.chinacdc.cn>). SARS-CoV-2 can spread rapidly in the community contrarily to SARS CoV and MERS-CoV that have a higher mortality rate but a stronger nosocomial than community transmissibility. This is likely due to the fact that they cause a more severe clinical phenotype than COVID-19 [6]. It was reported that COVID-19 average incubation period is 5.2 days (95% confidence interval (CI), 4.1–7.0) with the 95th percentile at 12.5 days [22]. Another study estimated it at 6.4 days (95% CI, 5.6–7.7) [23]. The median age of COVID-19 cases ranges from 49 to 57 years [6] and median time from the first symptom to death is 14 days [24]. While a detailed clinical landscape continues to be established, the most common clinical symptoms of SARS-CoV-2 observed in patients were fever (87.9%), cough (67.7%) and fatigue (38.1%), whereas diarrhea (3.7%) and vomiting (5.0%) were occasional [24,25]. All patients had pneumonia and about half had dyspnea [26]. Some COVID-19 patients showed arrhythmia, acute heart injury, impaired renal function and abnormal liver function (50.7%) at admission [27,28]. In addition, there is evidence of ocular surface infection in patients with COVID-19 as SARS-CoV-2 RNA was detected in eye secretions of patients [29,30]. A retrospective case series study conducted on 214 infected patients from Wuhan showed that 78 (36.4%) patients displayed neurologic manifestations [31]. Furthermore, diminished ability to smell or taste observed in some patients [32,33] was found to result from a neurotropic or neurovirulent viral infection of the olfactory system [34]. The older population and individuals with underlying health complications as cardiovascular diseases and diabetes were reported to present the severe disease symptoms [35]. Children were found less vulnerable than the elder population [36,37]. Pregnant women may be more vulnerable to SARS-CoV-2 as this virus may alter the immune responses at the maternal-fetal interface, and affect the well-being of mothers and infants [38]. A retrospective study based on nine pregnant women infected by COVID-19 showed no evidence of intrauterine vertical transmission between mothers and infants in the late pregnancy [39]. To avoid SARS-CoV-2 newborns infections after birth, immediate prevention instructions should be implemented for these women and their neonates, including a 14-day isolation for newborns

and avoiding breast feeding during this period [40]. Laboratory findings showed typical CT results including bilateral pulmonary parenchymal ground glass and consolidated pulmonary opacities sometimes with a rounded morphology and peripheral lung distribution [41]. Ground-glass-like lung images are probably due to the severe inflammation of lung cells becoming unable to exchange carbon dioxide and oxygen after SARS-CoV-2 infection [42]. A recent study showed that SARS-CoV-2 could infect T cells explaining the lymphocytopenia commonly found in COVID-19 patients [43]. It was also observed that most critically ill patients infected with SARS-CoV-2 had elevated levels of inflammatory cytokines (IL-6 and IL-10) [44], indicating potential bacterial co-infection caused by dysregulated immune system [45]. Moreover, Nguyen team, by using *in silico* analysis, showed that genetic variability across the three major histocompatibility complex (MHC) class I genes (human leukocyte antigen [HLA] A, B, and C) may affect susceptibility to and severity of COVID-19 which need further experimental investigation [46].

### SARS-CoV-2 transmission

Understanding transmission pathways of SARS-CoV-2 has significant implications for intervention and prevention. It was initially suggested that Chinese patients infected with SARS-CoV-2 may have visited the seafood market in Wuhan City or may have consumed infected animals. However, further investigation revealed that some individuals contracted the COVID-19 without visiting the market. Indeed, an epidemiological study in early cases in this city showed that only 22% of patients were directly exposed to the marketplace, 32% of cases were in close contact with the suspected cases and 51% had no contact with either source [47]. This suggests a human-to-human transmission of the virus and an ability to propagate, resulting in disease clusters from a single index patient [48,49]. The WHO estimated the reproductive number ( $R_0$ ) of SARS-CoV-2 to range between 2 and 2.5, which is higher than SARS (1.7–1.9) and MERS (<1). This suggests that SARS-CoV-2 has a higher pandemic potential [50,51]. Three transmission ways of SARS-CoV-2 in humans were proposed with incubation times of 2–14 days: 1) contact with liquid droplets produced by infected patients and/or 2) close contact with infected individuals and 3) contact with surfaces and material contaminated with SARS-CoV-2 (<https://www.cdc.gov/coronavirus/2019ncov/about/transmission>). In experimental setups, infectious viruses could be detected up to 24 h on cardboard, up to 2–3 days on plastic and stainless steel and up to 3 h post aerosolization (van Doremalen et al. 2020). Certain scientists recently highlighted another possible transmission route, the airborne transmission through droplet nuclei (or aerosols), meaning the possibility of the disease spreading in much smaller particles from exhaled air, known as aerosols. They are suggesting that aerosols are also more likely than droplets to be produced by talking and breathing and might pose a higher probability of transmission than coughing and sneezing [52]. In lab experiments, infectious SARS-CoV-2 particles were detected in aerosols for 3 h [53]. Liu and colleagues at Wuhan University collected samples of aerosols in and around hospitals treating COVID-19 patients and found viral RNA from SARS-CoV-2 on protective apparel and floor surface and their subsequent resuspension. In this study, viral RNA concentration in aerosol samples was low (0–42 genomes/cubic metre of air) [54]. An American team studied the presence of SARS-CoV-2 in air samples and surfaces from 11 isolation rooms of COVID-19 patients and showed that many (63%) of air samples had evidence of viral contamination, with higher airborne virus concentration (2860 copies per cubic metre of air) [55]. It is noteworthy to mention that infectious viruses have not been recovered from aerosols in any study. In a recently published paper, ten air samples of patient rooms with



confirmed COVID-19 cases in the largest clinical hospital in Iran showed that all air samples were negative [56]. This may be because of air sampling processes damaging the viruses or because the virus does not resist easily to aerosolization process. Finally, given the general scientific knowledge about aerosol long distance indoor transport, aerosol scientists have proposed that airborne transmission of SARS-CoV-2 is most likely to occur in poorly ventilated spaces [57].

#### SARS-CoV-2 structure and cells infection

SARS-CoV-2 RNA genome is 29.9 kb [58]. It contains 14 open reading frames (ORFs), encoding 27 proteins. At the 5'-terminal region of the genome, the ORF1 and ORF2 encode 15 non-structural proteins important for virus multiplication. The 3'-terminal region of the genome encodes functional structural proteins, namely spike (S), envelope protein (E), membrane protein (M) and nucleocapsid (N), plus 8 accessory proteins [58,59]. Phylogenetic and computational genomic analyses suggest that to enter in host's cells, SARS-CoV-2 shares the same human cell receptor with SARS-CoV (ACE2), while MERS-CoV uses another (DPP4) [20]. ACE2 is an ectoenzyme anchored to the plasma membrane of the cells of several tissues, particularly in the lower respiratory tract, heart, kidneys and gastrointestinal tract [60]. A structure model analysis shows that SARS-CoV-2 binds ACE2 with above 10 folds greater affinity than SARS-CoV, and much higher than the threshold required for viral infection [61]. The Spike (S) protein (of about 150 kDa) is the major antigen presented on the surface of SARS-CoV-2. The S protein forms a transmembrane homotrimer protruding from the viral surface to attach to the host cellular receptor ACE2. S comprises two functional subunits: subunit S1 responsible for binding to the cell surface receptor ACE2 and subunit S2 responsible viral fusion to the cell membrane [62].

SARS-CoV-2 hijacks host cells (such as lung cells) by endocytosis [63,64]. First, S protein binds to the cellular receptor ACE2 [65]. This attachment is followed by activation of the S protein, which initiates fusion of the viral membrane with the membrane of the host cell [10]. This fusion allows the virus to enter the cells [66]. SARS-CoV-2 releases its genetic material into the cell cytoplasm where it is translated into the viral replicase polyproteins pp1a and 1ab. Pp1a and p1ab are then cleaved by viral proteinases to form functional non-structural proteins (NSPs) such as a helicase (Hel) and the RNA-dependent RNA polymerase (RdRp) which is responsible for replication of structural protein RNA [67]. The plus-stranded RNA genome of SARS-CoV-2 will serve to synthesize subgenomic negative-strand templates that serve as templates for mRNA synthesis. Structural proteins S1, S2, E, and M are then translated by ribosomes that are bound to the endoplasmic reticulum (ER) [68]. Viral nucleocapsids (N) are assembled from genomic RNA, followed by budding into the lumen of the endoplasmic reticulum (ER)–Golgi intermediate compartment (ERGIC) [69]. The nucleocapsids fuse with the virion precursor. Formed virions will then be transported from the ER through the Golgi apparatus to the cell surface via small vesicles and released from the cell through exocytosis [70] (Fig. 4).

#### SARS-CoV-2 diagnosis tests

Diagnostic tests were developed rapidly after the start of the SARS-CoV-2 outbreak allowing early recognition and detection of this novel virus. Nasopharyngeal swabs are the recommended specimen for molecular analysis. As of 19 March 2020, the CDC made oropharyngeal, mid-turbinate, and nasal swabs acceptable specimen types if nasopharyngeal swabs are not available (<https://www.cdc.gov/coronavirus/2019-nCoV/lab/guidelines-clinical-specimens.html>). Samples are collected from the upper respiratory tract (oropharyngeal and nasopharyngeal)

and lower respiratory tract (endotracheal aspirate, expectorated sputum, or bronchoalveolar lavage) of patients suspected SARS-CoV-2 infection [71].

At the initial stage of the outbreak, identification of COVID-19 cases mainly involved virus isolation from swabs and viral nucleic acid detection by RT-PCR-based SARS-CoV-2 RNA detection in respiratory samples. Enzyme-linked immunosorbent assay (ELISA) kits for detection of IgM and IgG antibodies against N and other SARS-CoV-2 proteins have also recently been made available. Several other diagnostic tests are developed to detect other regions of the SARS-CoV-2 genome or targeting RdRp, Hel, S, E and N genes [72]. Another easy-to-implement and accurate CRISPR–Cas12-based lateral flow assay for detection of SARS-CoV-2 from respiratory swab RNA extracts in just 30 min is under development [73]. Currently there are 628 SARS-CoV-2 tests commercially available or in development for the diagnosis of COVID-19 <https://www.finddx.org/covid-19/pipeline/>.

#### SARS-CoV-2 treatment

To date, no vaccines or therapies have been approved to treat any of the known human coronaviruses. The rapid global spread of COVID-19 has emphasized the need for the development of new coronavirus vaccines and therapeutics for this family of viruses. Treatment will reduce the economic impact on the world as SARS-CoV had a history of taxing the global economy 30 US \$ to 100 US \$ billion [74]. Since the beginning of the COVID-19 outbreak, the WHO has encouraged researchers all over the world to develop a cure for this disease. Here we present some of these initiatives that are still in early stages of development.

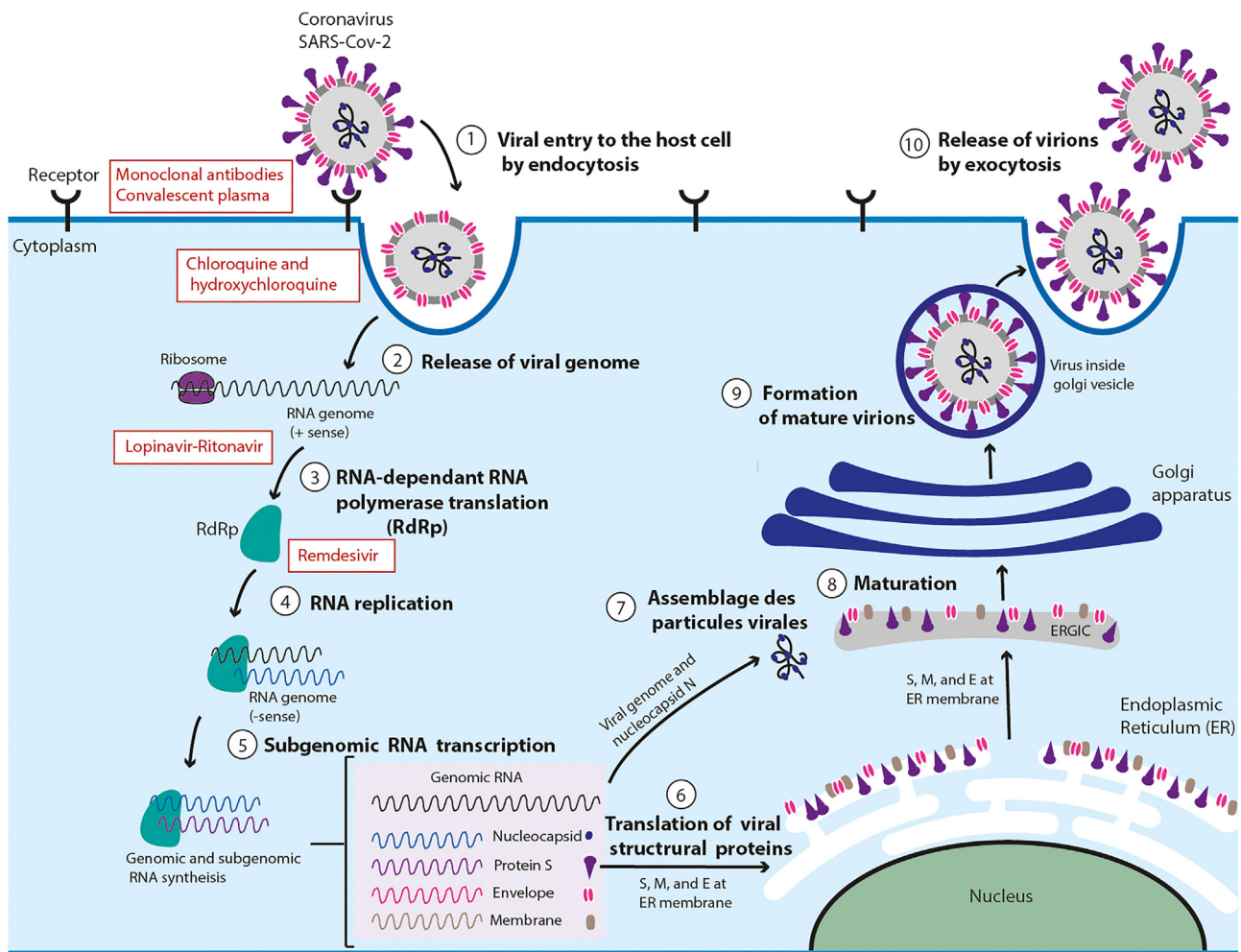
#### Antiviral agents

Randomized controlled trials were initiated and are being conducted for many antiviral agents. Lopinavir (LPV) was shown to inhibit the protease activity of coronavirus *in vitro* and in animal models and already used for SARS and MERS in combination with ritonavir, another antiviral drug [75,76]. However, a recent trial showed lopinavir-ritonavir has no treatment benefit for severely infected patients by SARS-CoV-2 [77]. Ribavirin is a guanosine analogue, used to treat several viral infections including those caused by the hepatitis C and respiratory syncytial viruses by targeting the RdRp complex [78]. Messenger RNA (mRNA) vaccine technology is also under development (in phase 1 clinical trial by the US National Institute of Allergy and Infectious Diseases) [79].

Remdesivir, a nucleotide analog antiviral inhibitor that may compete for RdRp, was designed for the Ebola virus and was with efficient against MERS and SARS [80]. Remdesivir has been reported to inhibit *in vitro* SARS-CoV-2 proliferation and therefore has clinical therapeutic potential [81]. Recently, Remdesivir was used in a clinical trial including 53 COVID-19 patients. Results showed clinical improvement in 36 of the 53 patients (68%). However, this drug needs to be used especially for patients not receiving invasive ventilation as the mortality rate was 18% when receiving ventilation, compared to 5% when not receiving [82].

#### Chloroquine and hydroxychloroquine

Chloroquine is antimalarial and autoimmune disease drug. It blocks viral infection by increasing endosomal pH limiting virus to cell fusion as well as interfering with the glycosylation of cellular receptor ACE2 [83]. Hydroxychloroquine is an analog of chloroquine. Both drugs have immunomodulatory effect and can suppress the immune response of IL-6 and IL-10 that have been reported to be increased in response to SARS-CoV-2 [84]. Clinical controlled trials have shown that chloroquine was proved to be effective in



**Fig. 4.** SARS-CoV-2 life cycle in infected cells and inhibition targets: SARS-CoV-2 begins its life cycle by binding of the S protein presented on the surface of the virus to the cellular receptor ACE2 on the target cell. After receptor binding, the S protein changes conformation, facilitating viral envelope fusion with the infected cell membrane through endocytosis. SARS-CoV-2 then releases its genetic material into the host cell. Genomic RNA is translated into viral replicase polyproteins pp1a and 1ab, which are then cleaved into small products by viral proteinases. By discontinuous transcription, the polymerase produces a series of subgenomic mRNAs that are translated into viral proteins. The positive-sense genomic RNA is then packaged into a ribonucleocapsid and is assembled into viral particles in the ER and Golgi apparatus where they undergo maturation. Virions are finally transported via small vesicles and released out of the cell through exocytosis. Inhibition targets are presented in red.

the treatment of COVID-19 by reducing pneumonia exacerbation and was included in the recommendations for the prevention and treatments of SARS-CoV-2 [85].

#### Corticosteroids

Corticosteroids could suppress lung inflammation but their use for the treatment of COVID-19 lung injury is not supported by clinical evidence as the clearance of viral infection is delayed and also due to the occurrence of side complications [86,87]. The WHO advises against the use of corticosteroids unless indicated for another reason [72].

#### Antibodies

The spike protein S is the principal target of antibodies. The SARS-CoV monoclonal antibody CR3022, a neutralizing antibody previously isolated from a convalescent SARS patient, was identified to bind potently with this protein [88]. This antibody may be a potential therapeutic candidate.

#### Convalescent plasma transfusion (CP)

Convalescent plasma transfusion (CP) therapy was successfully used in the treatment of SARS, MERS and during the 2009 H1N1

pandemic with acceptable efficacy and safety [89–91]. It consists of collecting convalescent plasma from patients 2 weeks after recovery, to ensure neutralisation and a high antibodies titer followed by its administration to infected patients. Duan and his colleagues (2020) performed a pilot study in three participating hospitals in China to explore the feasibility of CP treatment in 10 severe COVID-19 patients. They showed that clinical symptoms significantly improved with the increase of oxyhemoglobin saturation within 3 days, accompanied by rapid neutralization of viremia [92]. Another study performed on an uncontrolled case series of five critically infected patients, showed improvement in their clinical symptoms [93]. Despite CP being an effective way to improve survival rate of severely infected patients, it does not permit the patient to acquire a SARS-CoV-2 immune protection and the safety of plasma globulin products specific to SARS-CoV-2 deserves further consideration [94].

#### Global SARS-CoV-2 prevention measures

Given the lack of available effective vaccine or treatments, it is primordial to control the source of infection and cut off the transmission route of SARS-CoV-2 by implementing robust preventative measures against this virus. We know that close con-

tacts and fomites are the most common ways of transmission for SARS-CoV-2. Aerosol transmission is still controversial. The WHO recommended several standard procedures for slowing the spread of COVID-19 by raising awareness on the prevention and control of the disease in the general population. The bulk of these strategies involve restricting mass gathering by advising the population to be confined and avoid close contact with anyone showing symptoms of respiratory illness in order to decrease the risk of spreading by breaking the transmission chain. Thus, many countries suspended all types (cultural, social, religious, scientific, sporting, and political) of mass gatherings and opted for videoconferences, and telecommuting. The WHO also recommended to maintain personal hygiene especially regular hand washing with soap and water or hand sanitizer containing at least 60% alcohol, a healthy lifestyle and adequate nutritional intake [95]. Outside, people need to respect minimum 2 m social distancing and it is preferred to wear protective masks. To limit aerosol transmission, it is important to keep regular room ventilation and effective sanitization [24].

In the face of this pandemic, some countries showed good COVID-19 curve control because they rapidly deployed intense case finding measures to stop virus transmission. For example, South Korea dramatically slowed the epidemic by performing more than 300 000 diagnostic tests (5,828.6 tests per million) in the 9 weeks after the first case was described. Individuals who tested positive were identified and isolated [96]. Singapore used a broad case definition, aggressive contact tracing, and isolation by testing all patients with pneumonia and influenza-like illnesses in primary care settings and hospitals, severely sick patients in intensive care, and deaths with a possible infectious disease [97]. Taiwan and Hong Kong used similar strategies [98].

## Conclusion

The international alert about the COVID-19 infection has helped in the containment of SARS-CoV-2. At the date of writing, COVID-19 showed promising signs of ending. Many countries seem to be efficiently controlling this SARS-CoV-2 pandemic wave and have considerably limited the mortality rate thanks to knowledge garnered in the past from SARS and MERS epidemics, allowing for the rapid institution of more efficient preventive measures. However, SARS-CoV-2 is far from being eradicated and many researchers predict novel waves in the future. That is why research efforts on SARS-CoV-2 and COVID-19 need to be redoubled to discover efficient treatments as soon as possible. Several promising competitive therapeutic options are currently under development all over the world but require time to for validation and commercialization. There is still much to learn about COVID-19 and it critical that scientist around the world collaborate and share information in order to face this new global threat and to develop a suitable cure to benefit all of humanity.

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## Ethical approval

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## Author contributions

The order of topics in the article was designed by Mbarka Bchetnia & Catherine Laprise. Mbarka Bchetnia performed the literature review and writes the first version. Caroline Duchaine, Catherine Girard & Catherine Laprise contributed to the content, revised and approved the manuscript as well as this final version for publication.

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## References

- [1] Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: origin, transmission, and characteristics of human coronaviruses. *J Adv Res* 2020;24:91–8.
- [2] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 2020;382:727–33.
- [3] Corman VM, Lienau J, Witzentrat M. Coronaviruses as the cause of respiratory infections. *Internist (Berl)* 2019;60:1136–45.
- [4] Chang TH, Wu JL, Chang LY. Clinical characteristics and diagnostic challenges of pediatric COVID-19: a systematic review and meta-analysis. *J Formos Med Assoc* 2020;119(5):982–9.
- [5] Huang Y, Tu M, Wang S, Chen S, Zhou W, Chen D, et al. Clinical characteristics of laboratory confirmed positive cases of SARS-CoV-2 infection in Wuhan, China: a retrospective single center analysis. *Travel Med Infect Dis* 2020;101606.
- [6] Petrosillo N, Viceconte G, Ergonul O, Ippolito G, Petersen E. COVID-19, SARS and MERS: are they closely related? *Clin Microbiol Infect* 2020;26(6):729–34.
- [7] Munster VJ, Koopmans M, van Doremalen N, van Riel D, de Wit E. A novel coronavirus emerging in China - key questions for impact assessment. *N Engl J Med* 2020;382:692–4.
- [8] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;151(264–9):W64.
- [9] Su S, Wong G, Shi W, Liu J, Lai ACK, Zhou J, et al. Epidemiology, genetic recombination, and pathogenesis of coronaviruses. *Trends Microbiol* 2016;24:490–502.
- [10] Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, function, and Antigenicity of the SARS-CoV-2 spike glycoprotein. *Cell* 2020;181(281–292):e6.
- [11] Wang H, Li X, Li T, Zhang S, Wang L, Wu X, et al. The genetic sequence, origin, and diagnosis of SARS-CoV-2. *Eur J Clin Microbiol Infect Dis* 2020;1–7.
- [12] Li C, Yang Y, Ren L. Genetic evolution analysis of 2019 novel coronavirus and coronavirus from other species. *Infect Genet Evol* 2020;82:104285.
- [13] Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020;579:270–3.
- [14] Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* 2020;395:565–74.
- [15] Kan B, Wang M, Jing H, Xu H, Jiang X, Yan M, et al. Molecular evolution analysis and geographic investigation of severe acute respiratory syndrome coronavirus-like virus in palm civets at an animal market and on farms. *J Virol* 2005;79:11892–900.
- [16] Wang LF, Shi Z, Zhang S, Field H, Daszak P, Eaton BT. Review of bats and SARS. *Emerg Infect Dis* 2006;12:1834–40.
- [17] Memish ZA, Mishra N, Olival KJ, Fagbo SF, Kapoor V, Epstein JH, et al. Middle East respiratory syndrome coronavirus in bats, Saudi Arabia. *Emerg Infect Dis* 2013;19:1819–23.
- [18] Raj VS, Osterhaus AD, Fouchier RA, Haagmans BL. MERS: emergence of a novel human coronavirus. *Curr Opin Virol* 2014;5:58–62.
- [19] Lam TT, Shum MH, Zhu HC, Tong YG, Ni XB, Liao YS, et al. Identifying SARS-CoV-2 related coronaviruses in Malayan pangolins. *Nature* 2020;583(7815):282–5.
- [20] Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. *J Virol* 2020;94.
- [21] Wang Y, Wang Y, Chen Y, Qin Q. Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures. *J Med Virol* 2020;92(6):568–76.



- [22] Li P, Fu JB, Li KF, Chen Y, Wang HL, Liu LJ, et al. Transmission of COVID-19 in the terminal stage of incubation period: a familial cluster. *Int J Infect Dis* 2020;96:452–3.
- [23] Backer JA, Klinkenberg D, Wallinga J. Incubation period of 2019 novel coronavirus (2019-nCoV) infections among travellers from Wuhan, China, 20–28 January 2020. *Euro Surveill* 2020;25.
- [24] Guan WJ, Zhong NS, Reply Clinical characteristics of Covid-19 in China. *N Engl J Med* 2020;382(19):1861–2.
- [25] Yang W, Cao Q, Qin L, Wang X, Cheng Z, Pan A, et al. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): a multi-center study in Wenzhou city, Zhejiang, China. *J Infect* 2020;80:388–93.
- [26] Wu D, Wu T, Liu Q, Yang Z. The SARS-CoV-2 outbreak: what we know. *Int J Infect Dis* 2020;94:44–8.
- [27] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–Infected pneumonia in Wuhan, China. *JAMA* 2020;323:1061–9.
- [28] Li Z, Wu M, Yao J, Guo J, Liao X, Song S, et al. Caution on kidney dysfunctions of COVID-19 patients. *medRxiv* 2020, <http://dx.doi.org/10.1101/2020.02.08.20021212>.
- [29] Xie HT, Jiang SY, Xu KK, Liu X, Xu B, Wang L, et al. SARS-CoV-2 in the ocular surface of COVID-19 patients. *Eye Vis (Lond)* 2020;7:23.
- [30] Zhang X, Chen X, Chen L, Deng C, Zou X, Liu W, et al. The evidence of SARS-CoV-2 infection on ocular surface. *Ocul Surf* 2020;18(3):360–2.
- [31] Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol* 2020;77(6):1–9.
- [32] Wolfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Muller MA, et al. Virological assessment of hospitalized patients with COVID-2019. *Nature* 2020;581(7809):465–9.
- [33] Spinato G, Fabbri C, Polesel J, Cazzador D, Borsetto D, Hopkins C, et al. Alterations in smell or taste in mildly symptomatic outpatients with SARS-CoV-2 infection. *JAMA* 2020;323(20):2089–90.
- [34] Xydakis MS, Dehghani-Mobaraki P, Holbrook EH, Geisthoff UW, Bauer C, Hautefort C, et al. S1473-3099(20)30293 Smell and taste dysfunction in patients with COVID-19. *Lancet Infect Dis* 2020, [http://dx.doi.org/10.1016/S1473-3099\(20\)30293-0](http://dx.doi.org/10.1016/S1473-3099(20)30293-0).
- [35] Niu S, Tian S, Lou J, Kang X, Zhang L, Lian H, et al. Clinical characteristics of older patients infected with COVID-19: a descriptive study. *Arch Gerontol Geriatr* 2020;89:104058.
- [36] Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, et al. SARS-CoV-2 infection in children. *N Engl J Med* 2020;382:1663–5.
- [37] Dong Y, Wang L, Burgner DP, Miller JE, Song Y, Ren X, et al. Infectious diseases in children and adolescents in China: analysis of national surveillance data from 2008 to 2017. *BMJ* 2020;369:m1043.
- [38] Liu H, Wang LL, Zhao SJ, Kwak-Kim J, Mor G, Liao AH. Why are pregnant women susceptible to COVID-19? An immunological viewpoint. *J Reprod Immunol* 2020;139:103122.
- [39] Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet* 2020;395:809–15.
- [40] Xu L, Yang Q, Shi H, Lei S, Liu X, Zhu Y, et al. Clinical presentations and outcomes of SARS-CoV-2 infected pneumonia in pregnant women and health status of their neonates. *Sci Bull (Beijing)* 2020;65(18):1537–42.
- [41] Chung M, Bernheim A, Mei X, Zhang N, Huang M, Zeng X, et al. CT imaging features of 2019 novel coronavirus (2019-nCoV). *Radiology* 2020;295:202–7.
- [42] Liu W, Li H. COVID-19: attacks the 1-beta chain of hemoglobin and captures the porphyrin to inhibit human heme metabolism. *ChemRxiv*; 2020.
- [43] Wang X, Xu W, Hu G, Xia S, Sun Z, Liu Z, et al. SARS-CoV-2 infects T lymphocytes through its spike protein-mediated membrane fusion. *Cell Mol Immunol* 2020;17(8):894.
- [44] Moore BJB, June CH. Cytokine release syndrome in severe COVID-19. *Science* 2020;368(490):473–4.
- [45] Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clin Infect Dis* 2020;71(15):762–8.
- [46] Nguyen A, David JK, Maden SK, Wood MA, Weeder BR, Nellore A, et al. Human leukocyte antigen susceptibility map for SARS-CoV-2. *J Virol* 2020;94(13):e00510–20.
- [47] Li R, Tian J, Yang F, Lv L, Yu J, Sun G, et al. Clinical characteristics of 225 patients with COVID-19 in a tertiary Hospital near Wuhan, China. *J Clin Virol* 2020;127:104363.
- [48] Phan T. Genetic diversity and evolution of SARS-CoV-2. *Infect Genet Evol* 2020;81:104260.
- [49] Riou J, Althaus CL. Pattern of early human-to-human transmission of Wuhan 2019 novel coronavirus (2019-nCoV), December 2019 to January 2020. *Euro Surveill* 2020;25.
- [50] Chen TM, Rui J, Wang QP, Zhao ZY, Cui JA, Yin L. A mathematical model for simulating the phase-based transmissibility of a novel coronavirus. *Infect Dis Poverty* 2020;9:24.
- [51] Liu Y, Gayle AA, Wilder-Smith A, Rocklöv J. The reproductive number of COVID-19 is higher compared to SARS coronavirus. *J Travel Med* 2020:27.
- [52] Lewis D. Is the coronavirus airborne? Experts can't agree. *Nature* 2020;580:175.
- [53] van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. *N Engl J Med* 2020;382:1564–7.
- [54] Liu Y, Ning Z, Chen Y, Guo M, Liu Y, Gali NK, et al. Aerodynamic analysis of SARS-CoV-2 in two Wuhan hospitals. *Nature* 2020;582(7813):557–60.
- [55] Santarpia JL, Rivera DN, Herrera V, Morwitzer MJ, Creager H, Santarpia GW, et al. Transmission potential of SARS-CoV-2 in viral shedding observed at the University of Nebraska Medical Center. *medRxiv* 2020, <http://dx.doi.org/10.1101/2020.03.23.20039446>.
- [56] Faridi S, Niazi S, Sadeghi K, Naddafi K, Yavarian J, Shamsipour M, et al. A field indoor air measurement of SARS-CoV-2 in the patient rooms of the largest hospital in Iran. *Sci Total Environ* 2020;725:138401.
- [57] Morawska L, Cao J. Airborne transmission of SARS-CoV-2: the world should face the reality. *Environ Int* 2020;139:105730.
- [58] Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, et al. A new coronavirus associated with human respiratory disease in China. *Nature* 2020;579:265–9.
- [59] Malik YS, Sircar S, Bhat S, Sharun K, Dhama K, Dadar M, et al. Emerging novel coronavirus (2019-nCoV)-current scenario, evolutionary perspective based on genome analysis and recent developments. *Vet Q* 2020;40:68–76.
- [60] Imai Y, Kuba K, Ohto-Nakanishi T, Penninger JM. Angiotensin-converting enzyme 2 (ACE2) in disease pathogenesis. *Circ J* 2010;74:405–10.
- [61] Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science* 2020;367:1260–3.
- [62] Letko M, Marzi A, Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. *Nat Microbiol* 2020;5:562–9.
- [63] Qinfen Z, Jinming C, Xiaojun H, Huanying Z, Jicheng H, Ling F, et al. The life cycle of SARS coronavirus in Vero E6 cells. *J Med Virol* 2004;73:332–7.
- [64] Weiss SR, Navas-Martin S. Coronavirus pathogenesis and the emerging pathogen severe acute respiratory syndrome coronavirus. *Microbiol Mol Biol Rev* 2005;69:635–64.
- [65] Rabi FA, Al Zoubi MS, Kasasbeh GA, Salameh DM, Al-Nasser AD. SARS-CoV-2 and coronavirus disease 2019: what we know so far. *Pathogens* 2020;9.
- [66] Simmons G, Zmora P, Gierer S, Heurich A, Pohlmann S. Proteolytic activation of the SARS-coronavirus spike protein: cutting enzymes at the cutting edge of antiviral research. *Antiviral Res* 2013;100:605–14.
- [67] Zhavoronkov A. Geroprotective and senoremediative strategies to reduce the comorbidity, infection rates, severity, and lethality in gerophilic and gerolav infections. *Aging (Albany NY)* 2020:12.
- [68] Shin JS, Jung E, Kim M, Baric RS, Go YY. Saracatinib inhibits middle east respiratory syndrome-coronavirus replication in vitro. *Viruses* 2018:10.
- [69] Stertz S, Reichelt M, Spiegel M, Kuri T, Martinez-Sobrido L, Garcia-Sastre A, et al. The intracellular sites of early replication and budding of SARS-coronavirus. *Virology* 2007;361:304–15.
- [70] Masters PS. The molecular biology of coronaviruses. *Adv Virus Res* 2006;66:193–292.
- [71] Corman VM, Landt O, Kaiser M, Molenkamp R, Meijer A, Chu DK, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. *Euro Surveill* 2020;25.
- [72] Zhai P, Ding Y, Wu X, Long J, Zhong Y, Li Y. The epidemiology, diagnosis and treatment of COVID-19. *Int J Antimicrob Agents* 2020:105955.
- [73] Broughton JP, Deng X, Yu G, Fasching CL, Servellita V, Singh J, et al. CRISPR-Cas12-based detection of SARS-CoV-2. *Nat Biotechnol* 2020;38(7):870–4.
- [74] Smith RD. Responding to global infectious disease outbreaks: lessons from SARS on the role of risk perception, communication and management. *Soc Sci Med* 2006;63:3113–23.
- [75] Yao TT, Qian JD, Zhu WY, Wang Y, Wang GQ. A systematic review of lopinavir therapy for SARS coronavirus and MERS coronavirus-A possible reference for coronavirus disease-19 treatment option. *J Med Virol* 2020;92(6):556–63.
- [76] Zhu S, Guo X, Geary K, Zhang D. Emerging therapeutic strategies for COVID-19 patients. *Discoveries (Craiova)* 2020;8:e105.
- [77] Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of Lopinavir-Ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med* 2020;382(19):1787–99.
- [78] Elfiky AA. Ribavirin, remdesivir, Sofosbuvir, Galidesivir, and Tenofovir against SARS-CoV-2 RNA dependent RNA polymerase (RdRp): a molecular docking study. *Life Sci* 2020;253:117592.
- [79] Ahmed SF, Quadeer AA, McKay MR. Preliminary identification of potential vaccine targets for the COVID-19 coronavirus (SARS-CoV-2) based on SARS-CoV immunological studies. *Viruses* 2020:12.
- [80] Gordon CJ, Tchesnokov EP, Woolner E, Perry JK, Feng JY, Porter DP, et al. Remdesivir is a direct-acting antiviral that inhibits RNA-dependent RNA polymerase from severe acute respiratory syndrome coronavirus 2 with high potency. *J Biol Chem* 2020;295(20):6785–97.
- [81] Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res* 2020;30:269–71.
- [82] Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate use of remdesivir for patients with severe Covid-19. *N Engl J Med* 2020;382(24):2327–36.
- [83] Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, Ksiazek TG, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. *Virol J* 2005;2:69.
- [84] Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: an old drug against today's diseases? *Lancet Infect Dis* 2003;3:722–7.
- [85] Gao J, Hu S. Update on use of chloroquine/hydroxychloroquine to treat coronavirus disease 2019 (COVID-19). *Biosci Trends* 2020;14(2):156–8.

- [86] Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet* 2020;395:473–5.
- [87] Shang L, Zhao J, Hu Y, Du R, Cao B. On the use of corticosteroids for 2019-nCoV pneumonia. *Lancet* 2020;395:683–4.
- [88] Tian X, Li C, Huang A, Xia S, Lu S, Shi Z, et al. Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody. *Emerg Microbes Infect* 2020;9:382–5.
- [89] Cheng Y, Wong R, Soo YO, Wong WS, Lee CK, Ng MH, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. *Eur J Clin Microbiol Infect Dis* 2005;24:44–6.
- [90] Zhou J, Liu JH, Jin Y, Ouyang XL, Yang LG. [Protective effects of DMSO on function of lyophilized human platelets]. *Zhongguo Shi Yan Xue Ye Xue Za Zhi* 2007;15:1284–8.
- [91] Hung KT, Berisha SZ, Ritchey BM, Santore J, Smith JD. Red blood cells play a role in reverse cholesterol transport. *Arterioscler Thromb Vasc Biol* 2012;32:1460–5.
- [92] Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. *Proc Natl Acad Sci U S A* 2020;117(17):9490–6.
- [93] Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. *JAMA* 2020;323(16):1582–9.
- [94] Mair-Jenkins J, Saavedra-Campos M, Baillie JK, Cleary P, Khaw FM, Lim WS, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. *J Infect Dis* 2015;211:80–90.
- [95] Chakraborty I, Maity P. COVID-19 outbreak: migration, effects on society, global environment and prevention. *Sci Total Environ* 2020;728:138882.
- [96] Korean Society of Infectious Diseases, Korean Society of Pediatric Infectious Diseases, Korean Society of Epidemiology, Korean Society for Antimicrobial Therapy, Korean Society for Healthcare-associated Infection Control and Prevention, Korea Centers for Disease Control and Prevention. Report on the epidemiological features of coronavirus disease 2019 (COVID-19) outbreak in the Republic of Korea from January 19 to March 2, 2020. *J Korean Med Sci* 2020;35:e112.
- [97] Lee VJ, Chiew CJ, Khong WX. Interrupting transmission of COVID-19: lessons from containment efforts in Singapore. *J Travel Med* 2020;27(3):taaa039.
- [98] Wang CJ, Ng CY, Brook RH. Response to COVID-19 in Taiwan: big data analytics, new technology, and proactive testing. *JAMA* 2020, <http://dx.doi.org/10.1001/jama.2020.3151>.